The Special Pathogens of Concern
2017-2018
Learning Objectives

- Explore those pathogens that may warrant treatment in a biocontainment unit
- Describe the clinical presentation of selected special pathogens or high consequence infectious diseases
  - 2 broad categories:
    - Viral hemorrhagic fever (VHF)
    - Highly pathogenic respiratory viruses
- Understand principles of infectious disease transmission
Please note that this is not meant to be a comprehensive review of all special pathogens.

1. What is a special pathogen

2. Clinical presentation and management of Viral Hemorrhagic Fever (VHF)
   - Examples of Ebola and Crimean Congo Hemorrhagic Fever

3. Clinical presentation and management of selected highly pathogenic respiratory viruses
   - MERS, SARS and H7N9 influenza
What is a Special Pathogen?

- No explicitly defined terminology:
  - Special Pathogen
  - Highly Infectious Disease
  - High Consequence Infectious Disease
  - Highly Hazardous Communicable Pathogens

- No master list of pathogens
  - But there are some defining characteristics
The Special Pathogens: Infectious, Highly Hazardous, and Communicable
Who Does the BCU Protect?

- Patient
- Families
- Other Patients
- Laboratory Personnel
- Community
- Healthcare Workers
What is a Special Pathogen

- Pathogen associated with high morbidity and/or mortality
- Pathogen with high likelihood of secondary cases (person-to-person spread)
- Absence of an effective vaccine or prophylaxis or treatment
- Pathogen for which clinical or public assuredness concerns might prompt the use of a biocontainment unit
What is a Special Pathogen

Most of the BSL-4 pathogens would be considered “special pathogens”

Broad categories

• Viral hemorrhagic fevers (VHFs)
• Others i.e. Variola
• Highly pathogenic respiratory viruses?
## The Special Pathogens

### BSL-4 Pathogens

<table>
<thead>
<tr>
<th>Filoviridae</th>
<th>Arenaviridae</th>
<th>Flaviviridae*</th>
<th>Bunyaviridae</th>
<th>Orthopox viruses</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Ebola</td>
<td>• Lassa</td>
<td>• RSSE</td>
<td>• CCHF</td>
<td>• Variola</td>
</tr>
<tr>
<td>• Marburg</td>
<td>• Guaranito</td>
<td>• CEE</td>
<td>• Hantavirus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Junin</td>
<td>• TBE complex</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Machupo</td>
<td>• Kyasanur forest</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Sabia</td>
<td>• Omsk</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Vector-Borne; no known P-T-P transmission
All cause VHF except for Variola
Global hotspots for emerging infectious diseases that originate in wildlife
Global Rise in human infectious disease outbreaks

Viral Hemorrhagic Fever

- Crimean-Congo HF
- Dengue HF
- Venezuelan HF
- Hantavirus Pulmonary Syndrome
- Bolivian HF
- Argentine HF
- Lassa
- Yellow fever
- Rift Valley Fever
- Marburg Ebola
- Sabia
- Puumala
- Omsk
- Hantaan (HF w/renal)
- Kayasanur Forest
- Dengue HF

Legend:
- Filoviruses
- Flaviviruses
- Bunyaviruses
- Arenaviruses
Clinical Presentation and Management of Viral Hemorrhagic Fever (VHF)

VHF Misconceptions

- They all have the same features
- They all spread easily
- They are easily recognizable
- Bleeding is the primary cause of death
# Clinical Presentation and Management of Viral Hemorrhagic Fever (VHF)

## The Lethal VHFs

<table>
<thead>
<tr>
<th>Virus</th>
<th>Mortality Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ebola Zaire</td>
<td>65-90% *</td>
</tr>
<tr>
<td>Marburg</td>
<td>25-90%</td>
</tr>
<tr>
<td>Lassa</td>
<td>15-20% of hospitalized</td>
</tr>
<tr>
<td>CCHF</td>
<td>3-30%</td>
</tr>
<tr>
<td>RVF</td>
<td>50% with hemorrhagic form</td>
</tr>
</tbody>
</table>

*likely lower in well resourced countries
How contagious is Ebola?

How the Ebola virus compares with other contagious viruses. The reproduction rate or $R_0$, calculates the number of people likely to be infected by one person who has a disease.

<table>
<thead>
<tr>
<th>REPRODUCTION RATE ($R_0$)</th>
<th>Initial infected patient</th>
<th>Person he or she has infected</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 to 4 people</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 to 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 to 7</td>
<td></td>
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<tr>
<td>5 to 7</td>
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</tr>
<tr>
<td>6 to 7</td>
<td></td>
<td></td>
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<tr>
<td>12 to 18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 to 17</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**DISEASE**
- Ebola
- SARS
- Mumps
- Polio
- Smallpox
- Rubella
- Measles (Whooping cough)

**HOW IT SPREADS**
- Bodily fluids
- Airborne droplets
- Airborne droplets
- Fecal-oral route
- Airborne droplets
- Airborne droplets
- Airborne
- Airborne droplets

Sources: Michigan Center for Public Health; WHO; Transmission Dynamics and Control of Severe Acute Respiratory Syndrome, Nature; Understanding the Dynamics of Ebola Epidemics, National Institute of Health
EVD: Differential Diagnosis

Initial symptoms are non-specific

Other possible infectious causes of symptoms

- Malaria
- Typhoid fever
- Meningococcemia
- Dengue
- Influenza
- Lassa fever
- Sepsis
- Other bacterial infections (e.g., pneumonia)

PCR testing may be negative early in the course of illness
EVD: Human-to-Human Transmission

- Infectiousness of Ebola Virus Disease (EVD)
  - Infected persons are not contagious until onset of symptoms
  - Infectiousness of body fluids increases as patients become more ill
  - Remains from deceased infected persons are highly infectious

- Human-to-human transmission of Ebola Virus via inhalation has not been demonstrated
  - However, respiratory protection (e.g. N-95, PAPR) are recommended in case there is an unexpected need to perform an aerosol-generating procedure (e.g. emergency intubation)
Clinical Presentation of VHF

<table>
<thead>
<tr>
<th>Early Phase</th>
<th>Symptoms</th>
<th>Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fever</td>
<td>Minimal</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Myalgia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Abdominal Pain</td>
<td></td>
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Clinical Presentation of VHF

### Early Phase

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<td>Myalgia</td>
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</tr>
<tr>
<td>Abdominal Pain</td>
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</table>

### Late Phase

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bloody emesis</td>
<td>Shock</td>
</tr>
<tr>
<td>Bleeding from mucosa</td>
<td>Petechiae</td>
</tr>
<tr>
<td>Rash</td>
<td>Edema</td>
</tr>
<tr>
<td>Confusion</td>
<td>Pharyngitis</td>
</tr>
</tbody>
</table>

**Non-specific**

Maintain high index of suspicion

**Critically Ill**
EVD: Early Clinical Presentation

**Exposure**
- Fevers
- Chills
- Myalgia
- Malaise
- Rash

**Incubation period**
- 2-21 days
- Non infectious

**Symptom improvement**
- Nausea
- Vomiting
- Diarrhea
- Abdominal pain

**Survival**
- Hemorrhage
- Altered mental status
- Respiratory Failure
- Renal Failure
- Death

Day 0 10 15
EVD in Well Resourced Environments

Average 3L/day

Patients who receive care in a BCU:
18% mortality at 28 days

Profound electrolyte disturbances

Clinical Presentation and Management of Viral Hemorrhagic Fever (VHF)

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Clinical Presentation and Management of Viral Hemorrhagic Fever (VHF)
The Impact of Nutrition and Electrolytes

- Patients may have marked electrolyte abnormalities and nutritional deficiencies
  - Hypokalemia, hypocalcemia and hyponatremia
  - Both intravenous and oral replacement
  - Used oral nutritional supplements including nutritional drinks high in easily absorbed proteins, minerals and vitamins

- Laboratory testing for chemistries was **critical** to provide supportive care
Ebola Virus Disease (EVD): Managing Critical Illness

- No proven EVD-specific organ support beyond established CCM “best” practices for most infections
- Lung protective ventilation & minimizing sedation as possible
- Target euvoolemia
- Nutrition support – early & aggressive
- Delivery of critical care requires special consideration/planning
Ebola Virus Disease: Recovery

Prolonged convalescence in Ebola

• Includes arthralgia, myalgia, uveitis, abdominal pain, extreme fatigue, and anorexia

• Prolonged arthralgia and myalgia

• Depression, headache, skin sloughing, and hair, vision, and hearing loss have also been reported
There is a differential diagnosis when patients present

- Some have presented relatively well with fever, prodromal symptoms
- Some have become critically ill with multi-organ system failure
  - Need for emergent dialysis, intubation and mechanical ventilation
- Preparations should include plans for handling this range of illness until diagnosis of a serious communicable disease is either confirmed or ruled out
  - Additional considerations for range of ages possible from infants to older adults
Crimean Congo Hemorrhagic Fever

Rapidly Progressive MOF:
- Hematuria
- Purpura
- Liver failure
- Respiratory failure

Death

Tick Bite

RN exposure

Rash
- Transaminitis
- Vaginal bleeding
- Respiratory failure
- Renal Failure

Ribavirin

- Clinical improvement
- Viremic clearance

Crimean Congo Hemorrhagic Fever

Clinical Presentation and Management of Viral Hemorrhagic Fever (VHF)

Licensed Therapy and Prophylaxis

- Ribavirin for Lassa Rx
- YF-Vax for Yellow Fever Prevention
### Beyond the VHF's: Other Special Pathogens

<table>
<thead>
<tr>
<th>Family</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronaviruses</td>
<td><strong>SARS, MERS-CoV</strong></td>
</tr>
<tr>
<td>Henipiviruses</td>
<td>Nipah, Hendra</td>
</tr>
<tr>
<td>Orthopoxviruses</td>
<td>Smallpox, Monkeypox</td>
</tr>
<tr>
<td>Highly Pathogenic Influenza Viruses</td>
<td><strong>H7N9</strong></td>
</tr>
<tr>
<td>Bacteria</td>
<td>Pneumonic Plague</td>
</tr>
<tr>
<td>Mycobacteria</td>
<td>XDR-TB*</td>
</tr>
</tbody>
</table>
Mechanisms of Transmission

**Contact or Fomites:**
- Ebola
- Marburg
- Lassa
- Other VHF
- Variola
- Monkeypox

**Droplets:**
- Ebola
- Marburg?
- Nipah
- Hendra?
- Influenza
- Monkeypox
- Plague

**Droplet Nuclei:**
- Variola
- XDR-TB
- SARS?
- MERS?
Clinical Presentation and Management of Selected Highly Pathogenic Respiratory Viruses

The Coronaviruses

Causes of the Common Cold

- 229E
- NL63
- OC43
- HKU1
- MERS
- SARS
SARS

- Produces severe lower respiratory tract illness
- Appeared in China in 2002
- Ultimately affected 37 nations, including US & Canada
- No reported cases since 2004
- 8273 total cases recorded
  - 775 deaths
  - 27 US cases (no deaths)
- Overall mortality was 9.6%
Clinical Presentation and Management of Selected Highly Pathogenic Respiratory Viruses

SARS

- Clinical features:
  - Incubation period 2-7 days
  - Initial flu-like illness
  - Then, severe viral pneumonia
  - Possible secondary bacterial pneumonia

- Laboratory features:
  - Liver dysfunction, rhabdomyolysis

- Reservoir host - civet cats
  - Risk comes from exposure to these cats
The Special Pathogens
MERS
Accessed 16 June 2017

CONFIRMED GLOBAL CASES OF MERS-COV 2012 - 2017

Number of cases reported

- 1 - 5
- 6 - 20
- 21 - 100
- 101 - 500
- 501 - 1000
- >1000

Disputed Areas

Total number of reported cases: 1032

Data Source: World Health Organization
© WHO 2017. All rights reserved
Map date: 28/06/2017

Accessed 16 June 2017
Novel Coronavirus Transmission

The Special Pathogens

Coronavirus

- 2002

Cross-species transmission

Palm civets and other animals traded in live-animal markets

SARS-CoV

~30 years ago

Cross-species transmission

MERS-CoV

Continuous

Zoonotic transmission

Community contact

Hospital patient

Nosocomial transmission

Health care personnel

Other patient

Nosocomial transmission

Zoonotic transmission
Clinical Presentation and Management of Selected Highly Pathogenic Respiratory Viruses

Novel Coronaviruses

• Clinical presentation
  • Fever
  • Cough
  • GI symptoms
  • Lymphocytopenia and thrombocytopenia
  • Acute Severe Hypoxic Respiratory Failure
## MERS Clinical Presentation

### Among 47 patients in Saudi Arabia

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>98%</td>
</tr>
<tr>
<td>Cough</td>
<td>83%</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>74%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>26%</td>
</tr>
<tr>
<td>Myalgias</td>
<td>32%</td>
</tr>
<tr>
<td>Abnormal CXR</td>
<td>100%</td>
</tr>
</tbody>
</table>

- 89% required intensive care
- 72% required mechanical ventilation

Clinical Presentation and Management of Selected Highly Pathogenic Respiratory Viruses

MERS Clinical Presentation

- Diagnosis by rRT-PCR
- Samples should be sent from:
  - Lower respiratory tract
  - Upper respiratory tract
  - Serum

Figure 2: Radiographs of the chest of patient 2
(A) Chest radiograph obtained on May 9 showed systematic consolidation of the upper right lung lobe. (B) On May 12, ground-glass opacity and consolidation could also be seen in the lower left lobe. Bilateral ground-glass opacities and consolidation were noted afterwards on May 17 (C) and May 17 (D).
MERS Clinical Presentation
MERS-CoV Outcomes

• As of August 2017: 2066 confirmed cases reported to WHO since September 2012
• 720 fatalities (35%)
• Milder cases may not be confirmed via testing
• Older age and medical co-morbidities are risk factors for fatal disease

http://www.who.int/emergencies/mers-cov/en/
Influenza Virus

- Hemagglutinin
  Allows the flu virus to adhere to the respiratory tract

- Neuraminidase
  Allows the flu virus to escape from respiratory cells after replication
Risk Factors for Novel Influenza Emergence

- Pigs harbor human strains
- Pigs harbor avian strains
- Pigs thus serve as “mixing vessels”
- Antigenic shift occurs in the pig
- The fear: a new virus with human affinity and avian mortality
Clinical Presentation and Management of Selected Highly Pathogenic Respiratory Viruses

Relevance: Is it really going to be another VHF

Human Infection with a Novel Avian-Origin Influenza A (H7N9) Virus

Ebola Mortality Rate Compared to Recent Epidemics

- Avian flu: 60%
- Ebola: 50%

Other diseases:
- Spanish flu: 2%
- SARS: 9.6%
- Hong Kong flu: 0.1%
- Swine flu: 0.03%
The eight genes of the H7N9 virus are closely related to avian influenza viruses found in domestic ducks, wild birds and domestic poultry in Asia. The virus likely emerged from "reassortment," a process in which two or more influenza viruses co-infect a single host and exchange genes. This can result in the creation of a new influenza virus. Experts think multiple reassortment events led to the creation of the H7N9 virus. These events may have occurred in habitats shared by wild and domestic birds and/or in live bird/poultry markets, where different species of birds are bought and sold for food. As the above diagram shows, the H7N9 virus likely obtained its HA (hemagglutinin) gene from domestic ducks. Its NA (neuraminidase) gene from wild birds, and its six remaining genes from multiple related H9N2 influenza viruses in domestic poultry.
Clinical Presentation and Management of Selected Highly Pathogenic Respiratory Viruses

H7N9: Relevance

- 1500 confirmed cases
- 571 deaths
- Initially Low Pathogenic Avian Influenza strains (LPAI)
- Recent strains of Highly Pathogenic Avian Influenza (HPAI)
- Known person-person transmission
- Neuraminidase Resistance
Avian Influenza: Symptoms

Fever: 100%
Cough: 80%
Fatigue: 60%
GI symptoms: 10%
Avian Influenza: Clinical Presentation

Clinical Presentation and Management of Selected Highly Pathogenic Respiratory Viruses

- Pneumonia: Mean p/f: 144
- ARDS
- Shock
- AKI
- Rhabdomyolysis: 26%
- Mechanical Ventilation
- ICU admission
- Death
Clinical Presentation and Management of Selected Highly Pathogenic Respiratory Viruses

Avian Influenza: Deaths

- Hypoxemia
- Bacterial Superinfection
- Arrhythmia
- Acute heart failure
Clinical Presentation and Management of Selected Highly Pathogenic Respiratory Viruses

The Andromeda Strain

Patients with unknown diseases could be admitted to a Biocontainment Unit or an Ebola Treatment Center.

At the time of their initial outbreaks, these could have been “Andromeda Strains”

- Nipah
- Hendra
- SARS
- MERS
- Sin Nombre
- Many others
Overall: Providing Clinical Care in High-Level Isolation Units

- Relatively limited diagnostic testing
  - Laboratory tests
  - Imaging tests
    - Portable x-rays require advance planning/protocols
    - Use of point of care ultrasound for diagnostic imaging and procedure guidance

- Invasive procedures in PPE
  - Threshold may be different – response time to deteriorating patient is longer in isolation due to PPE donning
  - Emergent procedures more likely to lead to exposures
  - Consider simulation exercises of procedures – central line placement, endotracheal intubation

- Consider telemedicine based consultations when possible
  - Limit the number of providers who need to enter the patient room